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THE DIGHT INSTITUTE

of the University of Minnesota

Bulletin Number 5, 1947

A Report of the Dight Institute
FOR THE YEAR 1945–46

Four Generations of Blindness

Published for the Dight Institute by
THE UNIVERSITY OF MINNESOTA PRESS, Minneapolis

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AMERICAN FOUNDATION
FOR THE BLIND INC.

THE DIGHT INSTITUTE
of the University of Minnesota

A Report of the Dight Institute for the Year 1945–46

by Clarence P. Oliver, Director

WITH

Four Generations of Blindness

by J. C. Lysen and C. P. Oliver

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FIFTH ANNUAL REPORT OF
The Dight Institute
FOR THE ACADEMIC YEAR 1945–46

AN examination of a person's family history can often be used to his advantage. If he is disturbed by the presence of a deleterious trait in his family, a person can learn what the probability is that the trait will occur in himself or in his children, provided he will permit a geneticist to help him. In order to analyze the history, the geneticist has to collect information about the family, compare that history with histories in other families having a like characteristic, and determine the varied manifestations of the trait.

Genetic interpretations are based upon probabilities. It is not possible to state with certainty that a specific individual will have his familial trait unless some of the characteristics are actually observed in him, or unless his parents happen to have the same known recessive trait. Even though two persons have a similar defect, such as deaf-mutism, one cannot always be certain that they have a common hereditary type. The evidences indicate that there are two independent inherited types of deaf-mutism, each probably associated with a specific anatomical defect and each inherited recessively. Deaf-mutism caused by disease in early childhood is still another form of the defect and is not inherited.

Some environmental factors can lead to a defect in one person which seems to be identical to a trait that is hereditary in another. Geneticists have for some time recognized the effect of environment on their experimental forms, and evidences are being collected which substantiate the conclusion that the human may have certain defects solely because of environmental factors. This possibility must be considered when an analysis is being made of a family history.

The present bulletin reporting on the accomplishments of the Institute for the year 1945–46 includes some of the genetic analyses of family histories which have been made.

Minnesota Human Genetics League

As part of its program to assist in organizing groups interested in human genetics and eugenics, the Dight Institute and its advisory committee made plans for organizing and incorporating the Minnesota Human Genetics League. The certificate of incorporation was filed for record in the Office of the Register of Deeds, Hennepin County, Minnesota, on October 27, 1945. The purposes and objects of the League are to foster and develop all reliable and scientific means for the biological improvement of the human race; to initiate and support research in human genetics, eugenics, and population problems; to promote all educational programs for the wider dissemination of knowledge concerning human genetics, eugenics, and population problems; and to develop and promote public opinion favorable to the application of the results of research in human genetics, eugenics, and population problems.

The first annual meeting of the league, held November 14, 1945, in the Campus Club of the University of Minnesota, was attended by thirty-five members and guests. Officers elected for the year were: Dwight E. Minnich, president; Donald G. Paterson, vice-president; F. Stuart Chapin, vice-president; Clarence P. Oliver, secretary; and Theodore C. Blegen, treasurer. Directors elected were: for a term of one year, F. Stuart Chapin, Dwight E. Minnich, Clarence P. Oliver, and Donald G. Paterson; for a term of two years, Theodore C. Blegen, Richard M. Elliott, Walter A. Kenyon, and Irvine McQuarrie; for a term of three years, Mrs. F. G. Atkinson, Miss Helen Bunn, Mrs. John Cowles, and Mrs. Hill Shepardson. The league has seventy-one charter members.

Although the Dight Institute helped organize the Minnesota Human Genetics League, the two organizations are entirely independent. The Institute will continue its program of research in human genetics and make the information so gained known to society by means of publications, lectures, and consultation services. The league will establish its own program. The Institute will make its research facilities and services available to the league wherever that is possible.

Instructional Program

Although a number of the functions of the Institute might justifiably be considered parts of its instructional program, certain activities can definitely be so described. These include an annual lecture by some authority on human genetics, lectures by members of the Institute staff, and cooperation with specific groups in Minnesota.

ANNUAL DIGHT INSTITUTE LECTURE

In cooperation with the Minnesota Human Genetics League, the Dight Institute invited Dr. L. H. Snyder of Ohio State University to give the annual Institute lecture. Dr. Snyder's talk, "The Rh Factor in Feeblemindedness and Other Diseases," was given on the University campus on the evening of November 14, 1945. In his talk Dr. Snyder discussed the numerous blood groups and types now known which can be used to differentiate individuals. The 2560 different combinations of AB groups and the MN, P, S, and Rh types have practical value in medico-legal practice, particularly in tests for parentage.

The Rh blood types, the latest to be discovered, have another value to mankind. Not only may these types be important in transfusions, but they may occur in such combinations in mother and child that the child suffers ill effects. If the mother is Rh negative and the child Rh positive, an incompatibility of the blood types occurs and the effect may be an abortion or an erythroblastotic infant. Recent studies strongly suggest that some children who develop under the circumstances of Rh incompatibility may become feebleminded. This defect will not be inherited as such and is due entirely to the uterine environment. However, the environment is a result of the two Rh blood types, and the type which an individual has is a result of heredity, with Rh negative being recessive to Rh positive.

Dr. Snyder's lecture is published in *Minnesota Medicine,* February 1946. Reprints of this article are available at the Dight Institute.

LECTURES BY THE DIRECTOR

The Director has lectured on human genetics before twelve groups during the past year. Four of these lectures were used to explain how the analysis of a family history can be helpful to persons contemplating marriage or the production of children. In four other lectures our knowledge about hereditary factors in cancer was discussed. The other talks were miscellaneous in nature.

1. Premarital genetic examinations. One means of practicing eugenics is to study and make a genetic analysis of a person's family history. By this means one can often determine the probability that a certain marriage will lead to the production of a child with some undesirable characteristic. If the probability is too high, the examiner can call it to the attention of the individuals by comparing the probability with that of persons in other families. It is just as likely, however, that the analysis will show that the person cannot transmit the trait. The obvious effect will be to relieve the prospective mother of considerable worry. The family history of another person may indicate that she should postpone having children until later in life, or have them early, depending upon the circumstances of the history and the defect.

When one analyzes a person's family history, it is necessary first of all to determine whether the trait is due to environment or heredity. If heredity is a factor, one must then decide whether environment is strongly or weakly active in affecting the expression of the trait.

Some environmental factors are responsible for the development of specific traits in the human. For example, environment in the form of German measles in a woman during the early stages of pregnancy may cause the developing child to be born with certain eye defects, such as corneal opacity, microphthalmia, and cataract, or with defects of the heart, or with other anomalies. In other families similar defects are due to inheritance. It is necessary, therefore, to study the family carefully in order to determine whether either of these defects has a hereditary basis in that family. Another environmental factor, a parasitic protozoon, Toxoplasma, seems to be responsible for defects such as hydrocephaly and microcephaly and chorioretinitis in some families, and the infection may cause more than one member of a sibship to have the defect.

If environment is the active agency, the person need not worry about heredity in so far as that trait is concerned. This fact is important eugenically. If a person considers a trait to be hereditary when it is not, she may forgo bearing children when for the good of society she should have them.

Once the trait in a family is shown to be the result of heredity, an analysis of the family history may determine the probability that the trait will be transmitted to a child. If the characteristic is dominantly inherited, it will ordinarily occur in a person only if a parent is affected. Any child of any affected person will have a fifty-fifty chance of being affected. The short-finger condition known as brachydactyly has this type of inheritance. Exceptions to this rule occur, but the reasons can often be determined from a study of the family history. The exceptions may be traced to the late age of onset, as in cerebellar ataxia or Parkinsonism, or to varied manifestations of the condition, as in von Recklinghausen's disease. They represent errors in the methods used for the collection of records or in recognition of the defect.

A trait inherited recessively is more difficult to analyze. It is possible, however, to determine the probability that a relative of an affected person carries the potentiality to transmit a gene for the trait. In the close relatives of a person with a trait such as albinism or infantile family idiocy, this probability is significantly high enough that the individual should be advised not to marry a relative or another person whose family history shows a similar recessive hereditary anomaly. A normal sibling of an albino has one chance in two of being a carrier for the gene. A first cousin has one chance in four. For comparison, the chance any normal person in the general population has of being a carrier for the gene can be taken as one in fifty.

It is necessary, of course, to be certain that the traits in a parent and child are the same. A parent, for example, may have congenital absence of one or more of his permanent teeth, a trait occurring in approximately 5 per cent of the population (excluding the absence of wisdom teeth). His child with severe dental anomalies may have the same hereditary condition in more severe form, or he may have some other disease, such as anhidrotic ectodermal dysplasia, which has dental defects as one of its characteristics. Congenital absence of teeth and anhidrotic ectodermal dysplasia do not have the same method of inheritance.

Interrelationship between mother and fetus may also complicate making a genetic analysis of a family trait. This is true in some cases of feeblemindedness and in erythroblastosis (referred to in the annual lecture) and in mongolism (referred to under Consultation Services).

A geneticist can often help an individual recognize the possibilities of developing or transmitting the potentiality for a trait provided the person will supply a family history. It is necessary that the history be as accurate and as complete as one can make it. Sometimes the data are such that an accurate answer can be given. In other cases one can deal only with abstract probabilities. One must always recognize that the answer is based only upon what probably will occur and not very often upon what actually will occur in a given person.

2. *Heredity in cancer susceptibility.* Cancer is the reported cause of death for approximately 4000 Minnesotans each year. This high incidence has caused specialists in several fields of research to unite their efforts in the study of causes and possible controls of cancer. One factor under investigation is a possible hereditary tendency in certain families.

Cancer sometimes occurs in more than one member of a family. In some families the cancer incidence is so high that they are referred to as "cancer families," and are often cited as evidence that a hereditary tendency for cancer exists. Such family histories are not conclusive evidence for the influence of heredity. The disease is common enough so that runs can be expected in some families purely on the basis of random distribution of cases. Hereditary tendency can be studied only if sex, age, site of the cancer, and variable extrinsic factors are considered.

When cancer of a specific site is studied, familial trends seem to occur and this suggests a possible inherited tendency. Relatives of patients with carcinoma of the large intestine, gastric carcinoma, retinoblastoma, uterine cancer, and mammary cancer are more likely to have cancer of the same site than they are to have cancer of other organs. Among the patients with breast cancer, for example, approximately one half report that at least one male or female relative has had cancer. Approximately 50 per cent of the female cancerous relatives of breast cancer patients will have had carcinoma of the breast. Although this suggests a tendency for cancer of the breast to occur among relatives more frequently than might be expected by chance alone, the factor of heredity can be determined only after more detailed studies of the human families. Attempts have been made to study the incidences of cancer among the various relatives of cancer patients and to compare these with incidences among relatives of noncancerous persons. In such studies, however, ages of the members and effects of extrinsic factors must be considered or the data will have no value.

Extrinsic factors apparently have an effect upon the occurrence of most types of cancer. Certain occupations are critical in that sense in lung and skin cancer. Mammary cancer and uterine cancer are in some manner related to the marital and socio-economic status of women. Spinsters have a higher relative death rate from mammary cancer than do married women. Childless married women seem to have a higher rate than women with children. On the other hand, the relative death rate from uterine cancer is reported to be lowest in single women and highest in childless married women. The relative death rate from breast cancer also varies with the socio-economic status of women, those in the lowest group having the lowest relative rate. Since childbearing varies inversely with social status, the relationship might be explained on the basis of pregnancies.

It is true, however, that the total number of pregnancies does not seem to be related to the age of occurrence of breast cancer in women. In a study being made at the University of Minnesota, women with no pregnancies or with one, two, or more pregnancies have approximately the same age of occurrence of the cancer. All these women belong to a common socio-economic group.

Studies with mice clearly indicate that nursing is a factor to be considered in mammary cancer and that an activating agent is transmitted through the milk of the mother. The data on human beings is not yet complete enough for us to know the significance of nursing in human mammary cancer.

The evidence suggests that heredity is a factor in human susceptibility to cancer in some cases at least, and that extrinsic factors are also important. The possibility that heredity is a factor should not be alarming. If chance alone determined that a person would develop cancer, medical examinations of all people of certain ages would be necessary. If, however, hereditary factors are operative, special examinations can profitably be focused on individuals with family histories of cancer with special reference to site. These people would also recognize that they should seek regular examinations for the early recognition of the disease.

Research and Research Interests

The staff of the Institute recognizes that the study of human genetics is simplified by the united efforts of specialists in several fields. An individualist can carry on important investigations, but his progress will be slow. Our research projects represent cooperative efforts.

BREAST CANCER

The study of possible hereditary and environmental factors affecting human breast cancer has been continued during the year. This project, carried on in cooperation with a group from the Medical School of the University of Minnesota, has been supported principally by funds from the Graduate School.

Since the report of last year 108 new index cases have been added to the files, bringing the total to 272. Control cases, consisting of women with gallbladder disease, are now 47 in number. Index cases from the breast cancer patients and from the controls belong to the same socio-economic group.

In the cancer data analyzed to date, some of which need further checking for accuracy about relatives, 53 per cent of the index cases reported male and female relatives having cancer at various sites, although only 17 per cent of the index cases reported relatives having breast cancer. Forty-four per cent of the cancerous female relatives of the breast cancer patients likewise had carcinoma of the breast. In the population as a whole approximately 20 per cent of the females with cancer have carcinoma of the breast. Among the cancerous female relatives of the index cases, 52 per cent of the sisters, 41 per cent of the maternal and paternal aunts, and 33 per cent of the mothers had cancer of the breast. There is the suggestion in these data that siblings are more likely to have cancer of the same site than are mothers. The total incidence of breast cancer among the various relatives is low. Only 7 per cent of all the mothers of the index cases are reported to have had cancer, and only 2.5 per cent had cancer of the breast. Three per cent of the aunts and 3.5 per cent of the sisters (all ages included) of the index cases are reported to have had cancer of the breast. The incidence among these sisters will probably increase as they are followed throughout their lives.

The average number of pregnancies for the breast cancer patients is 3.6, or for those who were pregnant at least once, 4.2. Approximately 12 per cent of the pregnancies resulted in abortions. The average age at first pregnancy was 25.9 years. When the index cases are separated into groups according to number of pregnancies, ranging from 0 to 13 pregnancies, the average age of onset of breast cancer for each group is close to the mean figure for all the cases, 53.4 years.

CLEFT PALATE

In cooperation with the Crippled Children's Services of the Division of Social Welfare, the Institute has received 32 case histories of cleft palate for genetic analysis. The data are being collected by the public health nurses.

Of the index cases 19 are males and 13 females. Ten of the males and three of the females have one or more relatives with cleft palate. Parents were affected in only three of the cases. Most of the other relatives known to have had cleft palate belong in the groups of more distant relationship. The data are not yet sufficient to permit interpretation of the genetics involved.

Some investigators believe that the anomalies of cleft palate and missing upper lateral incisor teeth are closely related. In the families of the 32 cleft palate index cases, only six of the non-cleft palate relatives had any anomaly of the incisors. The incidence of congenital dental defects is no higher than that observed in the general population.

EPILEPSY

A study of extrinsic and intrinsic factors affecting epilepsy has been started. Miss Wynanda Moonen of the Institute staff is cooperating in this study with members of the University Hospital staff. The investigation will include a comparative study of the mentally normal and mentally deficient epileptic individuals. To date 60 index cases of epileptics are in the records.

FEEBLEMINDEDNESS

The analysis of the records of feeblemindedness which were given to the Dight Institute, referred to in earlier reports, has been completed. These records were collected and written up during the period from 1911 to 1918. They were specifically prepared for research. There are 566 separate histories, including several members of the same family. Of these, 545 have fairly complete family histories, and 121 are incomplete, although of considerable value in some aspects of the study of feeblemindedness.

The field workers who collected the original records visited the homes of the feebleminded persons and secured from the mother a developmental history of the patient and his siblings and the family history as completely as it could be supplied. Home conditions and immediate environment were observed directly by the worker when possible. Information was also secured from other relatives, neighbors, and official records. The patient was tested in most cases, and the mental age, sometimes the IQ, is included in the records.

Although the exact scientific accuracy of some of the family histories may be called into question, the workers appear to have been remarkably alert and well informed as to what would be pertinent information, and the care in assembling and recording the data probably could not be surpassed.

The age range of the index cases is from 22 months to 69 years. The mental age was given in 509 records. The lowest mental age recorded was three months and the highest was recorded as an IQ of 112. There are 129 who tested as idiots, with mental ages up to 3 years; 219 who tested as imbeciles, with mental ages up to 7 years; 139 who tested as morons, with mental ages up to 11 years; and 22 who tested more than 11 years, some classifying as high-grade morons. On the basis of a history of social inadequacy and personality difficulties, some of those who tested more than 11 years would be classified as psychopathic personalities.

The family histories of the index cases show that one or both parents were recorded as feebleminded in 214 cases. One or more sibs of the index cases were feebleminded in 207 cases; in this group 71 also had feebleminded parents. In 214 instances some of the non-feebleminded parents and siblings were reported to be dull, slow, lacking in force and judgment, or borderline. Some of these cases will fall into the groups classified as feebleminded; that is, one parent may be reported feebleminded and the other a borderline case. In 130 cases, however, the parents were either both feebleminded or both borderline cases.

In 49 histories the index case was the only feebleminded person in the family. In the other histories the number of feebleminded ranged from 2 in 36 family groups to as many as 65 in the large family groups. All together there are 1281 affected relatives of the index cases. This does not include those relatives recorded as borderline or otherwise abnormal. Ninety of the histories show blood relationship and 50 show intermarriage with one or more of the other histories.

Histories of nervousness, alcoholism, and poor social and home conditions are found throughout the family groups. Home conditions are marked unsuitable in at least 260 of the cases. Inadequate care of the index cases was recorded in a like number of cases. Keeping in mind that 130 of the index cases had both parents who were either feebleminded or borderline, one is not surprised by the number of cases of poor social and economic conditions which are recorded. A feebleminded parent can hardly be expected to give a child the best of care.

FAMILY RECORDS

During the year family histories of miscellaneous traits have been received from persons desiring to help in the study of human genetics. Twenty histories of hereditary conditions have been received, making a total of 113 now in these files. Together with the histories of dental defects, cancer, epilepsy, cleft palate, and feeblemindedness, all collected in research projects, the Institute now has approximately 1500 family histories in the files.

Some of the miscellaneous records collected this year are reported and interpreted in the following paragraphs.

1. Extreme dental deficiencies. In one family two of nine children have only a few of their permanent teeth. Two others are too young for information about their permanent teeth to be had. The trait apparently occurred with some degree of severity in one parent of the children, although it is not possible to examine him for the defect.

The index case, 15 years of age, has only eight permanent teeth and one unerupted bud. These include both upper central incisors, the upper left second molar, and the bud of the upper right second molar. In the lower arch the cuspid and first molar on the right and the cuspid, first premolar, and first molar on the left are present. Some of the deciduous teeth have been retained in both arches. A 22-year-old sibling has developed only five of her permanent teeth. They are the upper central incisors, the upper right first molar, and the two lower first molars. Deciduous teeth have been retained. Both girls look well nourished and healthy. They have firm, well-formed faces even though very few teeth are present.

The upper lateral incisors, lower central incisors, and second premolars are frequently congenitally absent. The deficiency occurs in several members of some families, and the histories indicate that heredity is a factor. Extreme deficiencies as reported in the present family, which include the absence of some of the more stable teeth, are found with certain diseased conditions, such as ectodermal dysplasia and some forms of epidermolysis bullosa. In the two siblings, however, there is no medical history of diseases of that type. Extreme cases of congenital absence of teeth are usually sporadic in nature. In some families, however, more than one member is found to be affected, and in the present family two siblings and probably one parent lacked most of their permanent teeth. Histories of this type strongly suggest that the trait is hereditary congenital absence of teeth in which the buds of most of the permanent teeth fail to develop. The method of inheritance cannot be determined definitely from the available family histories.

Another point of interest is found in these two cases. The roentgenographs show that root absorption of many of the retained deciduous teeth has occurred even though the permanent teeth have not formed. This is contrary to the belief that the formation of permanent teeth causes the absorption of the roots of deciduous teeth. Another peculiarity of the case is that a dental bud of the second molar tooth in the upper arch developed although the first molars failed to develop.

2. *Hemolytic icterus.* In a sibship of eleven members, a female has a gallstone, a large spleen, and a blood picture, as shown by laboratory tests, that characterizes hemolytic icterus. The affected person (the propositus) has three male children, two of them nonidentical twins. One of the twins and his non-twin sibling have hemolytic icterus, as shown by laboratory examinations. The normal twin has normal children. One of the affected members has a child reported to be anemic. None of the ten siblings of the propositus had the disease. The mother of the propositus was operated on for gallstones, but there is no information that she had hemolytic icterus.

The disease is considered to be dominantly inherited. It should therefore be recognized either clinically or by laboratory tests in a parent of any affected person. The propositus considers that she is the first one in her family to have the disease. If this is true, a mutation was responsible for its appearance in her. Once the mutation occurred, the gene would be transmitted to one half of her gametes on the average, and the disease could pass as a dominant trait to her children. The two affected sons have the potentiality to transmit the gene for the trait to their children, each child having a fifty-fifty chance of developing some sign of the disease.

3. *Muscular dystrophy.* In one family two teen-age males who are apparently identical twins have muscular dystrophy, probably the juvenile form of progressive muscular atrophy. The course of the disease has been very similar in the two. In one the shoulder muscles were first affected and now the arms are involved. In the other only the shoulder muscles are affected at the present time. Three sisters and one younger brother of the twins and all other members of the kinship are normal.

Muscular dystrophy does not have the same clinical manifestations in all affected persons. Where heredity is a factor, the method of inheritance may be dominant in some families, recessive in others, and sex-linked recessive in still others. The very similar course of the disease in the identical twins strongly suggests that inheritance is involved. Whether the dystrophy in this family has a recessive or sex-linked recessive type of inheritance cannot be determined from the family history.

4. Polydactyly. In one family history polydactylism can be traced through five generations. Eighteen of 73 members of the kinship have extra fingers and toes. Polydactylism is usually inherited dominantly. Exceptions to this rule are found in some Negro families as well as in some other families where the presence of extra digits is one of the characteristics of a more severe disease.

Only one exception to a dominant method of inheritance is found in the polydactylous family reported here. One member who was reported to have had normal fingers and toes produced five children all polydactylous. The affected members have very similar expressions of the trait. Each affected individual in the kinship had an extra finger on each hand and an extra toe on each foot.

5. Miscellaneous family histories. Several other family histories varying in degree of completeness have been received.

Congenital absence of upper lateral incisor teeth occurred in five members of a family; all but one had bilateral expressions of the trait. This anomaly occurs in approximately 2.5 per cent of the total population and may have varied expressions. The trait is dominant, but the gene is not always expressed.

Diabetes was reported in three family groups. In each one a dominant form of inheritance is suggested. Diabetes is reported by some workers to have a recessive inheritance. It seems more probable that it is dominantly inherited and the gene has a low penetrance, that is, it may be present without being manifested.

Ectopia lentis without arachnodactyly occurred in two siblings. The parents and other relatives are reported to be normal. This trait is dominantly inherited according to most authorities.

Hay fever is reported in several branches of one kinship, in both the maternal and paternal relatives of the propositus. With one exception the allergy occurred in an individual only if a parent had hay fever, and this one case may not be a real exception. The "normal" person died at an age younger than that at which one of his older siblings first recognized hay fever in himself. The history suggests a dominant inheritance; however, the effect of heredity in hay fever is not well understood.

Hay fever, asthma, and psoriasis have occurred in one kinship. In one branch hay fever and asthma can be traced through four generations, passing from father to children in two cases. The history suggests a dominant inheritance. In the other branch of the kinship psoriasis has occurred in three generations. In this family psoriasis is recognized early in life and is varied in manifestation. There is one instance of the trait passing through a normal person. Fortunately the marriage of the propositus uniting the two branches of the kinship did not bring the two irritating conditions together.

Multiple myeloma is reported in a propositus and one uncle. A hereditary basis for this cancer is not known.

Neurofibromatosis was present in two of five siblings and in one uncle of a kinship. The parents are reported to be normal. This disease has a dominant inheritance, but it may sometimes be present in a person and yet escape detection.

The genetics of certain other family histories are referred to in the following section.

Other traits for which the family histories require more complete data or descriptions have also been given to the Institute.

Consultation and Public Services

Human genetics is a very personal matter for anyone who is confronted with an undesirable hereditary characteristic in his own family. Yet in an analysis of this genetic problem a geneticist finds it necessary to think in terms of what is expected on the average to occur. The problem is simplified in some cases by recent progress in learning to recognize persons who have latent signs of some hereditary traits, as well as the knowledge gained that a trait in one person may be due to an environmental agent and not to gene action. There is still need for improvement in our methods and for an increase in our knowledge about hereditary traits.

When a geneticist attempts to analyze a family history for a specific person, it is necessary to make the answers as definite and personal as possible. This has been done for 53 persons during the year. In this report on the consultation services, more generalized answers to the questions are recorded in the hope that persons who have similar traits in their family histories may be helped to understand their problems.

MONGOLISM

Mongolism has been a disturbing problem to a sibling and also to a parent of a mongolian child. As is the usual case, only one mongolian child was reported in each kinship. Although mongolism is usually referred to as mongolian idiocy, certain studies show that some children with the defect can by training be developed into persons who are mentally low-grade normal. We should therefore refrain from using the term *idiocy* in describing the trait. The tendency to classify as mongol children only those who have the severest expression of the physical and mental characteristics probably causes some mongolian children to escape description. Much of the data about mongolism has been collected from the study of children who are in institutions.

It is difficult with the data on hand to determine what part heredity has in causing mongolism. Some investigators suggest that there is no involved hereditary factor. Most geneticists believe that a tendency to mongolism runs in certain families, but they are unable to describe the probable method of inheritance of this tendency. Family histories do not give enough data for a definite analysis, owing in part to the interacting environment and to the small number of children produced after a child with mongolism is born. Many mothers of mongols have no children after the defective child, although they may have the physiological ability to produce more children. The child with mongolism is, therefore, the "last-born." In some cases these mothers had hardly had time to bear another child at the time the history was reported. Other mothers admit that they definitely do not want another child and deliberately refrain from further childbearing. Some mothers of a mongolian child have subsequently produced normal children, whereas others have had at least one more child with mongolism.

One factor closely associated with mongolism is an increased age of the mother, although not all older childbearing women produce mongolian children. Mothers of mongols are on the average ten years older than are mothers of other children. The average age of the mothers of mongol children has been reported to be 39, and the chance any woman has to produce a mongol child increases rapidly with advancing age.

Because of the association between the age of the mother and the occurrence of mongolism, any woman having a close relative with the defect should be advised to have her children early in her life. If this is done, mongolism is less likely to occur in her child even if heredity is a factor. A mother who has produced a child with mongolism faces a different situation. It is not possible for anyone to tell her definitely the chance that another child will develop mongolism. She can be told, however, that in cases on record mongolism has occurred in more than one sibling in a family. Because of the peculiar relationship between uterine environment (associated with the age of the mother) and mongolism, this mother should recognize that she has reached that critical point in her life. Consequently she faces a hazard which other women do not have. The next child may be affected by the physiological condition of the mother provided that condition was not transitory. If heredity is a factor, the next child after one with mongolism may have the potentiality and develop the same defect, or he may lack that tendency and not have the trait, at least not so severe an expression of it.

CLEFT PALATE AND LIP

Cleft palate has been a problem to several persons. In a few cases a person has had the trait and wondered whether it might be expected in her child. In others the trait was expressed in grandparents or in siblings of a person wanting information about the anomaly.

Heredity probably is a factor to be considered in cleft palate. The inherited condition may be a delay in development in the fusion of the bones of the upper arch or it may be caused by some factor other than heredity which inhibits proper growth. How often accidental cleft palates occur is not known definitely, but some investigators suggest that only 25 to 40 per cent of cleft palates are due to inheritance.

The incidence of cleft palate is higher in children who have a parent with the anomaly than in children whose parents are normal. Considering those families with a history of the defect, the data indicate that a person with cleft palate will produce children with the anomaly twice as often as will a person who does not have the trait. If a person with a cleft palate has no known relative with the anomaly, the data are not sufficient for an accurate determination of the probable occurrence in the children. One investigator has suggested that approximately one person in 5000 has cleft palate.

Cleft palate sometimes skips one or more generations; a grandparent and a grandchild will have the defect, but the parent of the child will seem to be free of the trait. The inheritance, therefore, is not that of a simple dominant. However, the trait may be inherited dominantly with the gene having a low penetrance (not always expressed), or a varied expression so that some persons having the gene for the trait are not detected.

It seems probable that better physical examinations of the "normal" relatives of a person with cleft palate may show that some of them have slight defects which are not easily detected. These could be studied only with roentgen examinations.

The belief that congenital absence of upper lateral incisor teeth is associated with cleft palate does not seem to hold true. In an extensive study at the Institute of persons with the congenital absence of teeth, the incidence of relatives with cleft palate was negligible. In like manner, the proportion of anomalies of incisor teeth in relatives of cleft palate patients is, in a small study under way, no higher than that observed in the general population.

ICHTHYOSIS

Ichthyosis, sometimes called scaly-skin or fish-skin, may be inherited differently in various families. Some cases seem to have a dominant Mendelian type of inheritance. One type is thought to be linked in its inheritance with the Y chromosome and therefore occurs only in males, being transmitted from an affected male to all his sons. In other families the trait behaves as a recessive. In one family history brought to the Institute, the condition apparently occurs only in males and passes through females with normal skin to some of their sons.

A male in this family has dry skin. Gray scales are present on his arms, legs, and abdomen. If these scales are pulled off, one finds a coiled hair underneath. When the scaly part of the body is exposed to sunlight the scales gradually disappear, but they reappear when clothes are worn again. The condition is described as generalized, simplex ichthyosis.

The index case has two sisters who are free of the condition. His parents and grandparents also have clear skin, as have all his five maternal aunts. He has no maternal uncles. Other affected individuals are found only among his male maternal cousins who are children of his maternal aunts. One aunt has two sons, one of whom has the trait. Another aunt has five sons and one daughter; one of the sons has ichthyosis. A third aunt has one normal daughter and one son. The son has a very severe expression of the trait, according to the index case, but the scales occur only on the unexposed parts of the body. A fourth aunt has a normal daughter, and a fifth a normal daughter and a son who died in infancy.

The trait in this family occurs only in males. It has apparently passed through four sisters who are reported to be free of the condition. The appearance in four related sibships indicate that this ichthyosis is the result of heredity. The data are such that the trait could be explained as a recessive sex-linked trait or as a sex-influenced characteristic which is inherited like baldness. If the trait is sex-influenced, it could appear in the sons but not the daughters of the index case. If it is a sex-linked recessive, none of his children will show his trait, but he will transmit the gene to all his daughters. These daughters will be carriers and may have sons with ichthyosis.

MENTAL DEFICIENCY AND HYDROCEPHALY IN A FAMILY

In one family history, one child was mentally deficient and a second child who died early in life was reported to have had congenital internal hydrocephaly. Each of these traits can be produced in a person by environmental agencies. Hydrocephaly can be caused apparently by a parasitic infection of a child within the body of the mother. The active agent is Toxoplasma. In this family, however, the mother was shown by tests not to have toxoplasmosis. Feeblemindedness may be caused by incompatibility of the Rh blood types in the mother and child, but that is not true in this case. The mother is Rh positive. Environmental factors are therefore eliminated as causal factors of the defects in this family.

The family history also gives no evidence of either anomaly in any member of the kinship except the two children in the sibship. The two conditions may conceivably be related—that is, due to a common morphological anomaly—but there are no data to support such a conclusion. It is not possible to show that heredity is a factor in either of these cases. Each may be only an accidental occurrence or either may be the result of gene action. It is not possible to use the history in this family as a means of determining whether another child will have one or the other of the anomalies. One can say, however, that according to the result of some investigations a congenital anomaly in a member of a sibship increases the likelihood that a newborn child in that sibship will have a congenital anomaly. His chance is from five to ten times as great as that for a child born into a family where no congenital defects have occurred.

POLYCYSTIC KIDNEY

A person reported that his brother had polycystic kidney and died an early death because of it. The person wanted to know the probability that he would develop the disease or transmit it to his children. In the family the brother, mother, and maternal grandfather are reported to have died as a result of the disease. The disease was recognized early in the brother because of the clinical picture, and with this knowledge he did not marry. The mother also knew early in her life that she had the defect.

Polycystic kidney may escape detection in some persons at least until post-mortem examination. In this family, however, the clinical picture apparently is manifested and the disease is recognized early in life, some years before death.

The person in question has almost reached the age at which both his brother and mother died. At this age he has no sign of the disease in himself. It is very possible that he will remain free of the disease. There seems to be no reason why he should refrain from having children.

CANCER

Several individuals have wanted information about heredity in cancer. Particularly they have wanted to know whether the disease might develop in themselves if some relative had cancer. In general, one can say that a person who has a history of cancer among his close relatives should have regular medical examinations. The physician should always be informed about the family history.

The questions asked by one person clearly indicated a misunderstanding about the probable occurrence of cancer. This person had a lump in her breast. Some of her close relatives had had breast cancer. Apparently the person wanted suggestions in support of her belief that because several of her close relatives had cancer of the breast, the chance that her growth is malignant would consequently be lessened. Actually, with the presence of the lump and especially with her family history, the person should recognize the need to go to a competent physician who can determine whether the growth is malignant. It may prove to be nonmalignant, but if it is cancerous an early treatment is necessary. Because of her family history, the person's chance to develop cancer is at least twice as great as that of the average woman.

EPILEPSY

Two different individuals had questions about epilepsy. In one case the person's mother and brother are epileptic. The history suggests that the condition developed in this family because of a hereditary potentiality. The individual himself is old enough so that he is now less likely to show the symptoms of the disease. It is known, however, that not every person with a potentiality has recognizable signs of epilepsy. Some investigators have by the use of electroencephalograms found that certain relatives of epileptics do not have normal brain waves. This method of examination will be valuable to a person who has a close relative known to be epileptic.

In the other case the person was disturbed because he had an uncle who had convulsions. No other relatives in a large kinship were known to be epileptic. The history which was given strongly suggests that the convulsions in the uncle were the result of an injury. Under those conditions the logical assumption is that the trait is not a hereditary type, and the chance that the questioner will transmit a potentiality for that disease to his children is no greater than that of the average person.

OTHER CASES

Questions were also asked about other characteristics, including diabetes, frequent miscarriages in one family, hay fever, mental deficiency, migraine, multiple sclerosis, myopia, Parkinsonism, psychoses, retinitis pigmentosa, skeletal defects, and skin color.

Other Items

The Institute is continuing its competitive prize project in cooperation with the Minnesota Junior Academy of Science. In this project the Dight Institute offers a first prize of twenty-five dollars and one or more second prizes of ten dollars each to contestants who prepare the most accurate and complete family histories. The histories may be of a person's own family or of another family. Data forms and helpful suggestions can be had by writing to the Institute. In the contest the family histories are submitted to the secretary of the Junior Academy, who will in turn give them to the Institute. This project is to be carried on each year.

The Director of the Dight Institute has agreed to undertake with Dr. L. H. Snyder of Ohio State University a cooperative study of the genetics of breast cancer. For this purpose, a grant-in-aid has been made by the Committee on Growth of the National Research Council, which is acting for the American Cancer Society. The Institute has had a limited study under way and now can carry on the work more rapidly.

During the year the Director has cooperated with national groups interested in human genetics. He has served as a member of the Human Genetics Panel of the Committee of Growth and as a member of the Committee on Nomenclature for Human Genetics. On May 13 and 14 the Human Genetics Panel held its meeting at the Dight Institute.

Acknowledgments

The progress of the Dight Institute has been possible only because many individuals are interested in its program and are willing to give of their time. This help has been especially valuable to the Director during the period of organizing the Institute and establishing the research programs. To all the friends of the Dight Institute I extend my sincere appreciation.

CLARENCE P. OLIVER, *Director*

List of Publications

OLIVER, C. P., P. J. BREKHUS, and G. MONTELIUS. Anticipating dental problems caused by congenitally missing teeth. *North-West Dentistry,* 24:198–200. 1945.

OLIVER, C. P., P. J. BREKHUS, and G. MONTELIUS. Study of congenitally missing second premolars and space factors in the arches. *Journal of Dental Research,* 24:217–21. 1945.

OLIVER, C. P. Family history analysis as a help with personal problems. In press, *Proceedings Minnesota Academy of Science.*

OLIVER, C. P. Problems of human heredity, a project for the Junior Academy of Science. In press, *The Science Teacher.*

OLIVER, C. P. Human genetics in pediatric practice. In press, *Brennemann's Practice of Pediatrics.*

OLIVER, C. P., E. T. BELL, J. J. BITTNER, C. DENNIS, W. A. O'BRIEN, A. E. TRELOAR, and M. B. VISSCHER. Relationship between pregnancies and age of occurrence of breast cancer in the human. In press, *Minnesota Medicine.*

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Four Generations of Blindness

by J. C. Lysen and C. P. Oliver

EIGHT males in four generations of one kinship have been partially or completely blind. Six of these affected individuals attended a school for the blind during a period of sixty-four years. Although the recorded descriptions of the defects in the earlier cases are very incomplete, those for the more recent ones are complete and include a diagnosis of optic atrophy.

Many cases of optic atrophy have been reported since Leber accurately described the disease in 1871. The articles by Macklin (1) and Bell (2) review the cases in the literature. The earliest symptoms of optic atrophy vary in different individuals. Frequently the disease is characterized first by a retrobulbar neuritis, which soon gives way to signs of atrophy. A diminution of vision occurs in the center of the visual field and progresses rapidly for a period of time. Some power of vision usually remains in the periphery of the field and this vision may persist. Total blindness occurs only in some of the cases. In hereditary optic atrophy the defect is always bilateral with central scotomas present in both eyes, even though one eye may become affected earlier than the other. The age of onset of the disease also varies. The defect may first occur in the second, third, or fourth decades of life. Although considerable variation in the disease is observed, the course of the disease in the affected members of any one family tends to be the same.

Not all cases of optic atrophy can be said to be the result of heredity. In some of the families, however, the history of the disease indicates that heredity is a factor to be considered. In certain family histories the defect is transmitted directly from parent to child, suggesting a dominant type of inheritance. In a majority of the family histories optic atrophy is inherited as a sex-linked recessive trait, and most of the affected persons in these families are males. This is a result of the difference between the two sexes with respect to the x chromosome, the chromosome which carries any gene causing a sex-linked trait. A male has only one x chromosome and will as a consequence show any trait caused by the sex-linked gene he has. A female has a pair of x chromosomes and must have a pair of the genes before the trait will occur in her, provided that gene is completely recessive. A female can have optic atrophy of the sex-linked type only if her father had the defect. She will be homozygous, having received one recessive gene for the defect from her mother and the other recessive

NOTE. This is a report on K 123 in the Dight Institute files. Mr. Lysen is Superintendent of the Minnesota Braille and Sight Saving School at Faribault (formerly known as the Minnesota School for the Blind), and Dr. Oliver is Director of the Dight Institute.

gene from her affected father. In most histories, however, the mother of a son with optic atrophy does not have that disease. On the basis of present knowledge she is assumed to have normal visual acuity. She is nevertheless heterozygous (a carrier) for the recessive gene and each of her sons will have one chance in two of developing optic atrophy.

Familial Data for K 123

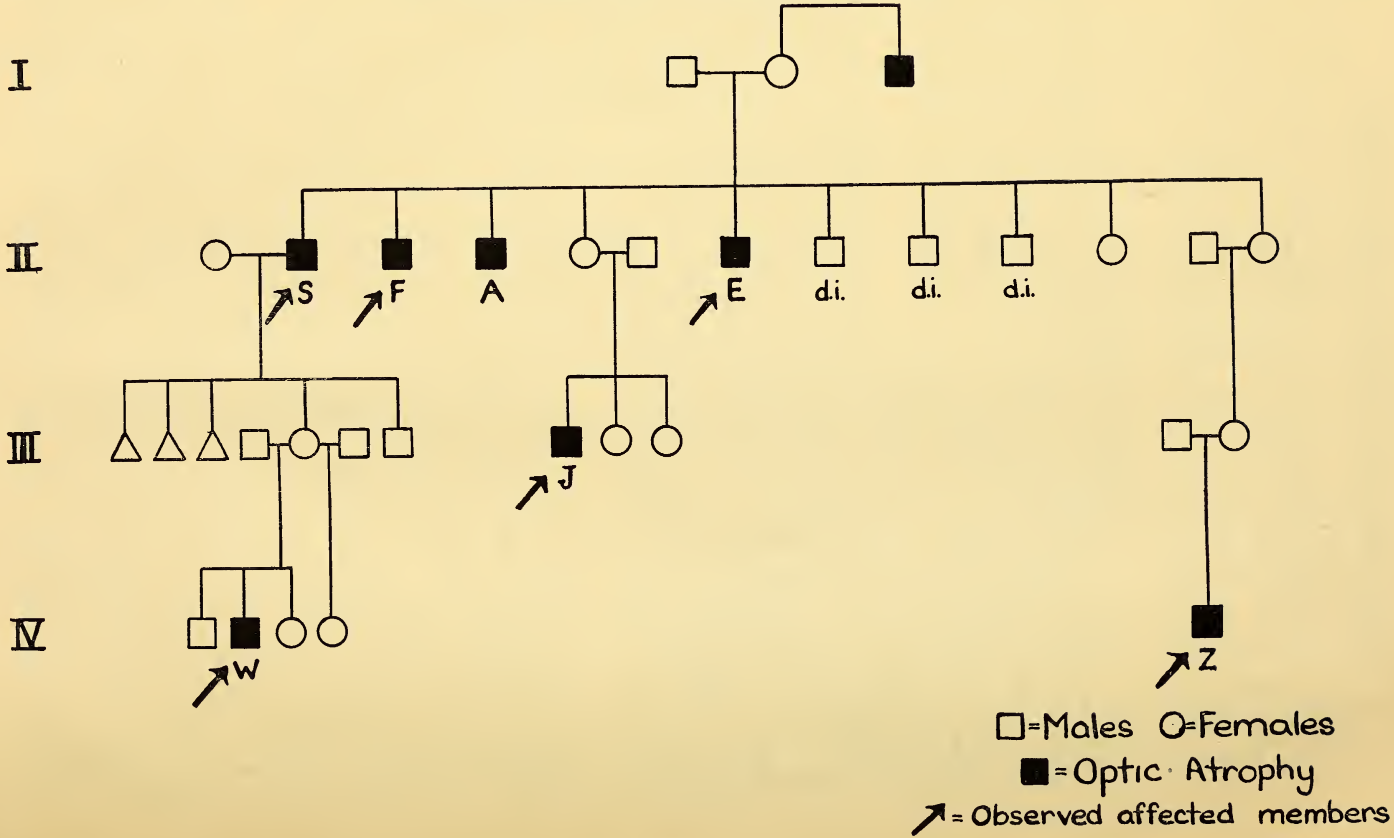
The members of a kinship with a history of optic atrophy are shown in the chart on page 22. Males are represented by squares and females by circles. Solid squares symbolize males with optic atrophy. Triangles indicate persons whose sex is unknown, and the symbol "d.i." means that the individual died in infancy. Letters are used to identify those members discussed in the text. Six of the affected members were examined upon their admission to a school for the blind.

Member W in generation IV was admitted to the school at the age of 16. A diagnosis was made of choroiditis and congenital optic atrophy. At the time of the examination W's vision was 1/60 in each eye. A Wassermann test was negative. It is of interest that during W's earlier life his parents considered him to be feebleminded. This proved to be untrue, because after W learned to use Braille his mental accomplishments were those of a normal individual. Apparently W's earlier lack of response to training was merely an expression of his inability to see well enough to read or do fine work. W has a brother, a sister, and a half-sister reported to have normal vision. Their parents, uncles, and aunts also were normal. W's recorded history shows that his maternal grandfather and a cousin were blind. This cousin had once been a student in the school.

Z in generation IV is an only child of normal parents. His record shows that when he entered the school he had congenital nystagmus, chorioretinitis, optic atrophy, and high-degree hyperopia. It is also stated in the record that Z probably never had complete vision. By the time Z was 14 years old the optic atrophy had progressed to total blindness. No ancestor of Z had optic atrophy, but two of his collateral relatives, the blind cousin and the grandfather of W, were recorded as having been "blind."

J in generation III of the chart was admitted to the school at the age of 10. At that time according to his record no vision was present in either eye. There was also evidence of a secondary cataract in the posterior chamber and a beginning of phthisis of the globe. J had two sisters with normal vision. None of his ancestors had the eye defect, and his record gave no evidence of any relative with atrophy. The records of both Z and W in generation IV refer to J as a cousin, and J's record shows that his mother was a sister of W's maternal grandfather.

A pedigree chart of optic atrophy in K 123. Squares represent males; circles, females; triangles, sex unknown; d.i., died in infancy. Solid squares indicate males with visual defect. The letters are used for references in the text.



The four affected members in generation II and the one in generation I have not been well described in the records. S, who entered the school at the age of 23, was reported to have become blind at 16. F, a brother of S, entered the school at the age of 18. According to the record his eyes became weak when he was 14. E, another brother, was admitted to the school at the age of 12. His record does not show when his eyes became defective, but the data in the records for F indicate that E was cross-eyed and partially blind when F entered the school, about nine years earlier than E's admission. The member in generation I was partially blind according to the records of F.

It is not possible from the available data to determine the definite ages of onset in the affected members of this family. However, the maximum ages of onset can be determined. These data are as follows:

Individual	W	Z	J	S	F	E
Maximum age	16	14	10	16	14	12

An error may be present in the data about E, whose record does not show the age at which the defect was recognized. Data collected from the records of F suggest that E had defects of vision at an early age, possibly 3, but the age at which he entered the school was 12, and this is used as the maximum age of onset for him. On the basis of these data the average age of onset is 13.66, which is younger than the 23.23 reported by Bell (2). The data do follow the familial tendency generally found with optic atrophy, that is, for the course of the disease to be the same in affected relatives.

Discussion of the Pedigree

All the affected members in the pedigree chart are males. The parents of each person with optic atrophy had normal vision and in each case the mother and not the father is the blood relative of the affected males. This is the type of family history which might be expected if the defect is inherited as a sex-linked recessive trait. Optic atrophy in this family falls into the most common group of eye defects, the one having a type of inheritance similar to that observed with hemophilia and red-green color blindness.

Since the gene for optic atrophy is localized on the x chromosome, a male with optic atrophy has only one gene for that trait. Any male with normal vision has a homologue, or allele, for that gene, and this gene is carried on his single x chromosome. The normal male cannot, therefore, transmit a gene for the defect to any of his progeny.

A woman who has a recessive gene for optic atrophy on one of her x chromosomes and an allele for non-optic atrophy on her other x chromosome will have normal vision. According to present knowledge, the normal allele completely dominates the recessive gene for the defect. Apparently it is not possible by present methods of examination to differentiate between such a woman who is heterozygous and one who has a pair of genes for normalcy. Occasionally the family history may be used to determine who are the heterozygous or "carrier" women.

The mother of W could have been told even before she had any sons that she was heterozygous for the recessive gene. Her father, S, would transmit his x chromosome to a daughter but not to a son, and since S had the recessive defect the gene for that defect would also pass to his daughter. Since W's mother was heterozygous each of her sons had one chance in two of developing optic atrophy. Her first son was fortunate, but W inherited his grandfather's trait through his mother.

Neither the mother of J nor the mother of Z had any way of knowing that she was heterozygous until she produced a son with the defect. Optic atrophy had not occurred in the ancestral line. However, a study of the history of the defect in the members of generation II would have shown that the chance of either woman being heterozygous was far greater than that of any woman in a family lacking a history of optic atrophy. In Z's case the gene passed through at least three women with normal vision before the appearance of the trait in himself. The fact that his great-grandmother produced sons with optic atrophy shows clearly that she was heterozygous. Although Z's mother and grandmother together had only one chance in four of being carriers for the gene, the development of optic atrophy in Z proved that the gene had been transmitted from the great-grandmother to the grandmother and then through the mother to Z.

Eugenic Consideration

It is possible in this family to determine the probability that any living member will have children with optic atrophy. In generation IV the brother of W does not have the gene for the defect and therefore will not have children with that trait. Since W's mother is heterozygous the chance that his sister received the recessive gene from her mother, and is therefore also heterozygous, is one in two. This will also apply to W's half-sister, since her normal father has no effect upon the transmission of the recessive gene for the trait. Each of the girls should recognize that they may produce a son with the defect, but no one can tell them with certainty whether they will have such a son. Any daughter produced by either of the two half-sisters will not have optic atrophy provided this daughter's father has normal vision. This daughter, however, may inherit the gene for the defect through her mother. W will have sons with normal vision since the recessive gene on his x chromosome will pass only to his daughters. However, each of his daughters will be a carrier. The interpretation in Z's case is the same as that for W.

In generation III the uncle of W is free of the defect and will not transmit it. J's chances are the same as those of W and the interpretation to be given for J's sisters is the same as that for the sisters of W.

In this family, as in any family with a history of a sex-linked recessive trait, the males with the condition normal for the trait can produce children without worry about transmitting the trait. The nonappearance of the defect in a male indicates that the trait in the family has ended in so far as he and his descendants are concerned. On the other hand, although a male with a sex-linked recessive trait will have sons and daughters who are normal for the trait, his grandsons or later male descendants through the female lines may develop the defect.

Women whose fathers have the defect will know that they are heterozygous. Even though a woman has no relative with the anomaly, once she produces a son with the defect she will know belatedly that she is heterozygous. A woman with collateral relatives having the sex-linked recessive trait but without an ancestor or son with that trait cannot know whether she is a carrier. She may be a carrier for the gene and yet as a matter of chance have only normal children. The knowledge may come to her after the harm is done, that is, after she or one of her female descendants has a child with the defect.

Summary

A history of optic atrophy is reported. The history indicates that the atrophy is inherited as a sex-linked recessive trait. Eight males in the kinship had the defect. The average maximum age at which the trait was recognized is 13.66 years. Eugenic considerations of the history are discussed.

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